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Myocardial disorganisation in hypertrophic cardiomyopathy
Another point of view

BARRY J MARON

From the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Historical perspective

Since the initial pathological description of hypertrophic cardiomyopathy by Dr Donald Teare in 1958[1] many of the clinical and morphological facets of this disease have been the source of controversy. In particular, the histological appearance of left ventricular myocardium in hypertrophic cardiomyopathy has often generated sharp differences of opinion.

Dr Teare originally described eight patients at necropsy who showed "bizarre and disorganized arrangement of muscle bundles" in an asymmetrically thickened ventricular septum. During the ensuing 25 years a number of histological or ultastructural studies emanated from laboratories in Great Britain and North America, based on the analysis of cardiac muscle obtained at necropsy, operation, or biopsy from patients with hypertrophic cardiomyopathy.[2–15] The vast majority of these investigations concluded that a disorganised arrangement of cardiac muscle cells in left ventricular myocardium (particularly the ventricular septum) was a characteristic morphological feature of patients with hypertrophic cardiomyopathy.[2–14]

Other authors have taken the view that disorganised cardiac muscle cells are neither typical of, nor particularly specific for hypertrophic cardiomyopathy.[16–20] For example, in the June 1982 issue of the *British Heart Journal*, Becker and Caruso[16] described a histological analysis of five non-diseased hearts, and concluded that cellular disorganisation (or disarray) was a normal morphological finding and had no diagnostic significance as a marker for hypertrophic cardiomyopathy. In their review Becker and Caruso presented their views with such enthusiasm as to leave the impression that myocardial disorganisation is not an important morphological feature of hypertrophic cardiomyopathy. For the innocent (but interested) bystander who is not a student of hypertrophic cardiomyopathy or an active investigator in this field, such divergent viewpoints must certainly constitute a source of confusion and frustration. In this paper I have attempted to identify the sources of this controversy and the areas in which it is possible to reconcile the vastly different perspectives regarding myocardial architecture in hypertrophic cardiomyopathy.

Definition of controversy

An important element of this controversy is the lack of consensus regarding what constitutes abnormal cellular arrangement in left ventricular myocardium. This problem of definition is accentuated by the fact that some non-diseased hearts or hearts with cardiac diseases other than hypertrophic cardiomyopathy contain areas of myocardium in which adjacent cardiac muscle cells are not arranged in precisely parallel alignment. The relative importance placed on minor deviations from parallel cellular arrangement has differed considerably among investigators. Though guidelines and histological criteria for normal cell alignment have been proposed,[9–14 17] the ultimate judgement as to whether a portion of myocardium shows "true" disorganisation has been dictated primarily by each investigator's perception that myocardial architecture deviates sufficiently from normal to justify labelling that particular area as pathological.

Such histological assessments will obviously be influenced largely by the investigator's own experiences and background. For example, some authors (including Becker and Caruso) have virtually confined their observations to subjects with normal hearts or with cardiac diseases producing secondary forms of left ventricular hypertrophy, and then extrapolated their findings to hypertrophic cardiomyopathy *without having studied any meaningful number of patients with hypertrophic cardiomyopathy*.[16–20] This scientific approach in which the investigator sees only "one side

of the coin" creates a narrow perception of the limits of normal and abnormal cellular arrangement, since the most extreme examples of cardiac muscle cell disorganisation (which occur in hypertrophic cardiomyopathy) have not been part of that individual's experience.

CARDIAC MUSCLE CELL DISORGANISATION AS A MARKER FOR HYPERTROPHIC CARDIOMYOPATHY

Several published investigations have been performed using study designs which rigorously conform to the basic principles of experimental observation, that is a reasonably sized experimental group (with hypertrophic cardiomyopathy) and a control group were both analysed in a similar and standardised fashion; each of these studies concluded that conspicuous cellular disorganisation was a characteristic and reliable morphological marker for hypertrophic cardiomyopathy.[9-14] The lack of a universally accepted histological definition for normal cellular arrangement seems to have less impact on the conclusions of these studies, which applied the same histological criteria for normality uniformly to all hearts in both the experimental and control groups.

Our experience in this area of investigation over the past 10 years has involved the detailed study of myocardium from a particularly large group of almost 100 patients with hypertrophic cardiomyopathy, as well as from over 400 patients with a variety of congenital or acquired heart diseases or normal hearts.[10 11 13 14] We have used a quantitative histological approach in which the area of a myocardial tissue section involved by disorganised cardiac muscle cells was calculated. Furthermore, patients with hypertrophic cardiomyopathy and control patients were studied in an identical fashion; in both groups tissue sections were taken from the same sites in the left ventricular wall, in the same plane of section, and the same criteria for normal and abnormal cellular arrangement were applied to each study group. Excluded equally in each of these groups was the type of cellular malalignment which is "normally" present in regions of myocardium exposed to particular stresses, that is at the edges of fibrosis or within trabeculations and at the point of covergence of major muscle bundles or ventricular walls.

With such a study design, we were able to show that patients with hypertrophic cardiomyopathy and patients with other cardiac diseases or normal hearts *differ distinctly* with respect to the histological appearance of left ventricular myocardium, that is that the extent and severity of cardiac muscle cell disorganisation in the septum and left ventricular free wall is most extensive and severe in hypertrophic cardiomyopathy. The vast majority of our patients with hypertrophic cardiomyopathy (about 95%) showed cardiac muscle cell disorganisation and this abnormal cellular arrangement occupied particularly large areas of myocardium. In contrast, cellular disorganisation was uncommonly present in patients with other cardiac diseases or normal hearts, and in these subjects the abnormal cellular alignment occupied extremely small areas of left ventricular myocardium which were unlikely to be of any pathophysiological import. To underline the enormous differences in the extent of cellular disorganisation between these two populations of patients it should be emphasised that in those with hypertrophic cardiomyopathy, an average of about 33% of the ventricular septal tissue section was disorganised, and that more than 50% of the section was involved in 25% of the patients. In patients with other diseases or normal hearts, an average of only about 1% of the tissue section was disorganised.

Becker and Caruso[16] have emphasised that different orientation of the tissue block and plane of section can lead to apparent differences in the extent of disorganisation. We also recognise the importance of plane of section in identifying disorganisation and have shown cellular malalignment to be far more extensive in tissue sections obtained transverse to the long axis of the left ventricule than in sections oriented parallel to the long axis.[10 14] Hence, the fact that demonstration of disorganisation may depend greatly upon the plane of sectioning should not be considered evidence that histological assessment of myocardium is of limited diagnostic value in patients with hypertrophic cardiomyopathy. On the contrary, awareness that the histological diagnosis of hypertrophic cardiomyopathy is made most optimally with transverse plane tissue sections is of obvious value from a diagnostic standpoint.

Conclusion

Dr Donald Teare's original histological observations on myocardial architecture in hypertrophic cardiomyopathy have been supported by studies from other laboratories, encompassing a large number of patients representative of the broad clinical and morphological spectrum of hypertrophic cardiomyopathy. The presence, *per se*, of cardiac muscle cell disorganisation is not pathognomonic or unique for hypertrophic cardiomyopathy and a small proportion of these patients show little or no disorganisation. The considerable extent, however, to which cellular disorganisation occurs in most patients with this disease has been defined in quantitative terms and this fact clearly distinguishes hypertrophic cardiomyopathy from other lesions producing left ventricular hypertrophy and from normal hearts. Hence, in this context, pronounced cardiac muscle cell disorganisation

does appear to have an important diagnostic use as a morphological marker for hypertrophic cardiomyopathy. Refutation of this principle will require standardised quantitative histological observations attained in sizeable numbers of patients with hypertrophic cardiomyopathy, as well as in patients with other cardiac diseases or normal hearts.

In addition to its value as a criterion for the histopathological diagnosis of hypertrophic cardiomyopathy, cardiac muscle cell disorganisation may provide the anatomical substrate for abnormal cardiac electrical and mechanical function in this disease. It seems worth while, therefore, to direct future studies of myocardial cell disorganisation towards an understanding of its pathophysiological role in the natural history of hypertrophic cardiomyopathy.

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Requests for reprints to Dr Barry J Maron, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 7B-15, Bethesda, Maryland 20205, USA.